In the Drawings:

Please accept the drawings included herewith as Figs. 1-12 and 15-16. Each of these drawings is a color photograph as described in the Brief Description of the Drawings. Each color drawing is included herewith in triplicate.

REMARKS:

Claims 44-66 remain for consideration in this application with claims 44, 46, 51, 58, 59, and 60 being in independent format. Claims 44 and 45 have been amended and claims 46-66 have been added.

To begin, applicants would like to thank the examiner for her time and courtesy in permitting and conducting an interview with myself and the inventors of the present application.

In the Office Action dated August 5, 2004, the specification was objected to for containing hyperlinks. The hyperlinks have been removed in the amendments to the specification. Accordingly, applicants assert that this objection has been overcome. Additionally, the title has been amended to more clearly indicate the claimed invention, the drawings have been resubmitted in color format, and the specification has been amended to reflect the color photographs contained in the application. Accordingly, applicants assert that these objections have been overcome.

The specification was also rejected to for referring to a disclosure document. This document was made a part of the application from which this application was derived and therefore, should form a part of this application as this parent application (S/N 09/573,080) was incorporated by reference in this application. Therefore, applicants assert that this objection has been overcome.

Claims 44 and 45 were rejected under 35 U.S.C. 112, first paragraph for lack of written description. To begin, applicants note that these are method claims, and are not product claims and that the term "breakpoint" has been replaced with "abnormality." It was expressly noted that the rejection was not for a lack of enablement of the recited

steps contained in the method claims. In other words, the specification enabled those of skill in the art to perform the recited steps. Applicants assert that the steps to perform the method do not change based on the probe or location within the genome. By enabling at least one example, those of skill in the art can apply the exact same methodology for ANY probe and/or breakpoint interval or structural abnormality. In the present application many examples were provided.

With respect to written description for determining breakpoints intervals and/or abnormalities, Example 1 provides a detailed description of the development of probes in accordance with the invention for methods using a single probe to determine the existence of a chromosomal abnormality. Those of skill in the art will also appreciate that, in some instances, hybridization of just a single probe using the methods of the present invention will also provide knowledge of the interval within which a chromosomal abnormality or breakpoint occurs. In Example 1, applicants taught the claimed methods by first analyzing GenBank for the HIRA gene. As described in the application, the HIRA gene is deleted from one of the two homologous copies of chromosome 22 in patients with DiGeorge or Velocardiofacial syndrome. Once the gene was selected, the sequence was compared with known repeat sequences, including SEQ ID Nos. 1-428 and 447-479. The steps used to make this comparison were provided in Example 1 and Table 1 was generated to show the locations and coordinates of repetitive sequence family members found in and adjacent to the HIRA gene. The intervals between the repetitive sequence family members were then selected for use as probes. Again, these steps are fully detailed in Example 1. The probes were amplified using PCR and labeled prior to hybridization. The hybridization steps were then described in detail

as were the "detection" steps. Results from this example, shown by Figs. 6 and 12, illustrate that breakpoints can be determined by such methodology. Specifically, the Fig. 6 photograph shows the probe hybridized to a single region of both chromosome 22s in a normal individual, whereas Fig. 12 illustrates one normal chromosome having the hybridization present and the other chromosome showing no hybridization, and thereby demonstrating that this second chromosome 22 contains a breakage interval spanned by at least the chromosomal coordinates of the set of probes that fail to hybridize to this chromosome. Because the location of the probes is known from the GenBank information (and their defined chromosomal coordinates), the minimum breakage interval is also defined. Any interval between two adjacent repetitive sequences could be used as a probe, as described in the present invention. Further written description is provided in Examples 2-5. Applicants note that the breakpoint referred to in the application actually refers to the interval within which the breakpoint (or abnormality as now claimed) occurs. This is possible because each probe of the present invention is defined by a unique set of genome coordinates (see Table 4). A breakpoint interval is therefore defined and understood by those of skill in the art as the smallest and largest genome coordinates found among both of the probes. Accordingly, the present invention determines the precise length and boundaries of breakpoint intervals.

Moreover, some GenBank entries also contain annotations that provide precise locations of breakpoints. Such information is useful in designing or selecting probes that would hybridize to opposite sides of a breakpoint. For example, the present invention used GenBank entry U07000 to design single copy probes that detect breakpoints in the BCR gene (when it fuses to ABL1 in chronic myelogenous leukemia or acute

lymphoblastic leukemia) and this entry contains breakpoint annotations. Here is an example of the type of coordinate-based information that is provided in the annotation of this GenBank entry:

> misc_feature 69807..69812
> /gene="BCR"
> /note="breakpoint region: 6 bp from chromosome 22 occur in
> both 9q+ and 22q- sequences at the breakpoint; patient FY
> with ALL (acute lymphoblastic leukemia)"

An important point to consider is that the number of probes actually set forth in the specification is representative to those of skill in the art as it is clear that the specification teaches how to obtain additional probes using no more than the steps provided in the application and the wealth of information available regarding genomic sequences. In determining the location or existence of structural chromosomal abnormalities, the number of probes is irrelevant as it is their spatial relationship to one another and to the location of the abnormality on the chromosome. Table 4 of the present application clearly shows the coordinates of many probes by referring to their GenBank accession number and comparing corresponding GenBank accession and genomic coordinates. Those of skill in the art are precisely directed where and how to obtain the probe sequences. Alternatively, if requested, applicants could amend the specification to include the sequences of as many probes as was necessary to satisfy the written description requirement. Such an amendment would not constitute new matter as the GenBank coordinates are provided for many of the probes in the specification. Accordingly, it cannot be said that the claims lack sufficient written description as the description clearly teaches those of skill in the art how to make and use probes in accordance with the invention and all of these claims are method claims.

Additionally, the present claims have been amended to recite that the abnormality is associated with a pathological condition or disease predisposition in an individual or their offspring and the claims detail the method by which the probes are identified. Such limitations are clearly supported by the examples of the present application and Table 4 in particular. In this Table, disruption of the ABL1 gene is representative of a structural chromosomal abnormality that contributes to the pathological condition of chronic myelogenous leukemia and the IC regulatory elements is disrupted in individuals with the pathological conditions of Prader-Willi Syndrome and Angelman Syndrome or those that are predisposed to having offspring with those pathological conditions. The claims further include the steps of identifying a probe sequence by ascertaining the nucleotide-by-nucleotide sequence of a target nucleic acid and comparing the ascertained sequences with SEQ ID Nos 1-428 and 447-479 using a computer program, and developing a probe comprising a sequence complementary to a non-repetitive portion of the target that hybridizes to at least a part of the identified genomic nucleic acid sequence. This differentiates the present claims from the prior art which required prehybridizing or cohybridizing the probes with unlabeled repetitive DNA sequences to provide hybridization specificity (e.g. masking or blocking cDNA such as Cot1 DNA). Such limitations reduce the number of probes that will be covered by claims of the present invention and the examples provided in the specification all describe probes that include such limitations. However, the present methods have been shown to provide increased sensitivity in comparison to the probes and methods of the prior art. For example, both Rowley and Croce were able to detect high reiteration repetitive sequences by screening of subclones with radioactively labeled genomic DNA. However, these methods were

unable to detect low reiteration repetitive sequences, which is something the present invention can achieve. By not detecting the low reiteration repetitive sequences, hybridization results can contain false positives when searching for single copy probes. Such a problem is solved by the present invention. Accordingly, for all of these reasons, applicants assert that these rejections have been overcome.

During as well as after the interview, a question arose regarding adequate support for the recitations "appearing up to three times in a haploid genome"; "localization coordinates"; hybridization coordinates"; and "surveying the public knowledge associated with said clinical or genetic etiology." The "surveying" phrase has been deleted from claim 52. "Appearing up to three times in a haploid genome" is supported in the specification as it would be understood by those of skill in the art because the specification refers to probes hybridizing to chromosomal DNA. As is known in the art, the diploid genome contains 2 copies of each chromosome and the haploid genome contains just a single copy of each chromosome. Accordingly, for copies of the probes to appear up to three times in the genome, as set forth in the specification at page 9, lines 14-18:

> In the context of the present invention, the term "single copy" with reference to a nucleic acid sequence refers to a sequence which is strictly unique (i.e., which is complementary to one and one only sequence in the corresponding genome) but also covers duplicons and triplicons. Stated otherwise, a "single copy" probe in preferred forms will hybridize to three or less locations in the genome.

Applicants were obviously referring to an organism's haploid genome. This is further supported by Example 5 at page 48 which states:

> Single copy probes developed from such regions, of course, lack known repetitive sequence elements. However the probes generally hybridize to all of the paralogous copies, since each of the copies remain hybridized even under the most stringent hybridization wash conditions. Because multiple, tightly clustered sites on the chromosome are hybridized in a specific interval, the hybridization signal produced from these hybridizations is brighter than that expected from a comparable probe sequence which was represented once per haploid genome. Thus, these genomic duplicons or triplicons increase the effective target size of the probe. This implies that shorter probes from such regions can produce hybridization signals comparable in intensity to those generated by longer probes. Selection of shorter probes from duplicated genomic domains will be particularly useful for development of probes for genomic regions where long single copy intervals are underrepresented.

Such a disclosure clearly shows that all references to the number of copies of probes refers to the number appearing in a haploid genome. "Localization coordinates" has been replaced with "sequence coordinates that define the position of the probe in reference to its location on a normal chromosome." Such a definition precisely defines what is meant by the claim and support is provided in the examples of the application. For more support, please refer to Table 4 which provides such sequence coordinates. "Hybridization coordinates" refers to the location on a chromosome or nucleic aid region that the probes developed using the methods herein hybridize to. Such hybridization is clearly shown in the drawings that accompany this application.

Similarly, applicants assert that new claims 46-66 also satisfy the written description requirement of 35 U.S.C. 112, first paragraph. New claims 59 and 60 are also supported in the specification. Specifically, page 8, lines 8-14 discloses that probes of the present invention may be used with any target nucleic acid that may contain repetitive

sequences. Accordingly, these claims are not limited to target regions of genomic DNA but may also, for example, include purified nuclear DNA, heteronuclear RNA, or mRNA. The steps of these claims are then described throughout the application and the examples therein.

Claims 44 and 45 were rejected under 35 U.S.C. 112, second paragraph, for being indefinite. The rejected phrase "single copy nucleic acid probes," which incorporated the objected term "repeat sequence," has been replaced with a more definite definition of the probes. Specifically, the probes are now defined by having at least 50 nucleotides, appearing up to three times in a haploid genome, being free of SEQ ID NOS 1-428 and 447-479, and comprising nucleic acid sequences from a set of known coordinates in the genome of an individual that lacks a structural nucleic acid abnormality within said target region of nucleic acid. Similar language also appears in the new claims. Thus, this rejection has been overcome.

The phrase "ascertaining the location of said breakpoint" has been amended to determining the existence of the abnormality. Thus, this rejection has been overcome.

Claim 45 has been further differentiated from claim 44 by reciting that the plurality of probes are distinct from one another. Moreover, the use of a plurality of probes from each side of an abnormality enables both a more precise localization of the breakpoint (or abnormality) interval, including situations where the breakpoint is not in the predicted target region.

New claims 46-66 do not contain any reference to the phrases that were referred to in the rejection under 35 U.S.C. 112, second paragraph. Accordingly, applicants assert that these new claims also satisfy the requirements of 35 U.S.C. 112, second paragraph.

The Office Action noted that claims 44 and 45 were not entitled to the priority of the parent application, Serial No. 09/573,080. Specifically, it was alleged that the parent specification did not support the broad concept of determining any chromosome breakpoint. These claims have been amended to recite "structural chromosome abnormality" rather than "breakpoint." Such a claim is supported at several locations within the parent specification. For example, page 30, line 6 of the parent application, recites "the probes developed from genomic sequences other than those presented as examples cited herein can also be utilized to detect inherited, sporadic and acquired rearrangements." Additionally, Examples 1 and 2 refer to pathological conditions that typically result from abnormalities other than translocations, which were acknowledged as taught in the parent specification in the Action. Specifically, Example 1 of the parent application describes probes for delineation of deletions, duplications, and supernumerary maker chromosomes from chromosome 22 (page 18, line 35 and page 19, lines 1-11). Example 2 describes probes for delineation of chromosomal deletions, duplications, and dicentric chromosomes (page 27, lines 22-33) on chromosome 15 and chromosomal deletions on chromosome 1. The parent application also discloses the use of combinations of multiple probes to detect deletions (page 27, lines 9-18 and page 29, lines 18-23), and that individual probes can be labeled with different labels to indicate the genomic representation of each of the sequences in a mixture (page 8, lines 8-12). Accordingly, one of skill in the art would understand that the parent specification teaches those of skill in the art more than the utility of probes in connection with translocations. Specifically, the description of the uses of probes of the present invention teaches those of skill in the art how to select a series of colinear probes from the same chromosome,

coupling some of them to one type of label (e.g. biotynylated-dUTP) and coupling the remainder to another type of label (e.g. digoxigenin-dUTP). If the sequences complementary to the biotin-labeled probes were deleted as a result of a structural chromosomal abnormality and the sequences complementary to the digoxigenin-labeled probes were not deleted on this same chromosome, then only the digoxigenin-labeled probes would be detected on that chromosome, whereas both would be detectable on an intact chromosome. Because both probes were designed directly from the known genome sequence and have precisely defined genomic addresses, those of skill in the art would infer that the deletion breakpoint (or abnormality) occurred between the coordinates specifying the set of digoxigenin labeled probes and the corresponding coordinates specifying the biotin labeled probes. The new claims cover similar subject matter and therefore also relate back to the parent application. Accordingly, applicants assert that all of the present claims are entitled to the priority of the parent application.

Claims 44 and 45 were rejected under 35 U.S.C. 102(e) and 102(a) as being anticipated by Rowley et al., (U.S. Patent No. 6,121,419) and under 35 U.S.C. 102(b) by Tanaka et al., (113 Cancer Genetics and Cytogenetics, 29-35 (1999)). The present claims have been amended to recite that the probes are genomic DNA probes. Rowley relies on the use of cDNAs, which are not genomic DNAs, but rather are derived from multiple exons without the intervening introns. Furthermore, it is well known by those of skill in the art that the untranslated regions of many cDNAs contain repetitive sequences (defined herein as SEQ ID NOS. 1-428 and 447-479). A search of [RefSeq] (mRNAs of all known, confirmed, curated human mRNAs in GenBank for the presence of just one of the specified sequences (SEQ ID NO. 2) revealed 197 different genes containing this

repeat alone. Presumably, if all of the repetitive sequences specified in the application were searched, additional cDNA sequences will be found that are not "Single copy" as defined in the application. Thus, unless hybridization of repetitive sequences in such cDNA probes are disabled with C_0t-1 DNA, the method of Rowley cannot be used universally (without additional experimentation) to detect breakpoints throughout the genome. Rowley does not determine if the cDNA probes are free of SEQ ID NOS. 1-428 and 447-479 prior to hybridizing cDNA to the chromosome. Accordingly, it cannot be said that Rowley anticipates the claims, as currently amended. The probes of Tanaka are not free of SEQ ID NOS 1-428 and 447-479, as required by the amended and new claims. In fact, every intron of AML1 includes at least some of these repetitive sequences as shown below in Figure A. This figure illustrates the distribution of these repetitive sequences as well as two known breakpoints in the human genome reference sequence of the AML1 gene. The restriction maps in Fig. 1 of Tanaka shows that the probes disclosed therein contain both introns and exons meaning that the probes themselves must contain the repetitive sequences shown in Figure A and therefore, are not free of SEQ ID NOS 1-428 and 447-479. Tanaka attempted to disable the hybridization of these sequences to chromosomes using C_0t-1 DNA suppression, since the presence of these repetitive sequences would have resulted in hybridization of these probes throughout the genome. Non-specific probe hybridization without such C_0t-1 DNA blocking would render these probes useless for detecting chromosome rearrangements. The most common repetitive sequences of the AML1 gene is of the SINE category which is among the most abundant class in the genome. This evidence of the existence of

repetitive sequences in Tanaka is also provided in declaration by Dr. Peter Rogan and Dr. Joan Knoll, which is attached to this amendment and response.

Additionally, applicants note that the independent claims presently pending in this application contain limitations regarding making or selecting a nucleic acid probe. These limitations were found to be novel and non-obvious by the U.S. Patent and Trademark Office for the "parent" application. Recently, U.S. Patent Number 6,828,097 issued in the name of the same inventors named herein and the present application is a continuation-in-part application of the application that issued as the '097 patent. Specifically, the present claims require identifying a genomic nucleic acid probe sequence by ascertaining the nucleotide-by-nucleotide sequence of a target nucleic acid sequence, comparing the ascertained sequences with the sequences of SEQ ID NOS: 1-428 and 447-479 in said target nucleic acid sequence using a computer program, identifying a sequence that is free of SEQ ID NOS: 1-428 and 447-479 from said comparison. Limitations similar to these resulted in the issuance of the '097 patent.

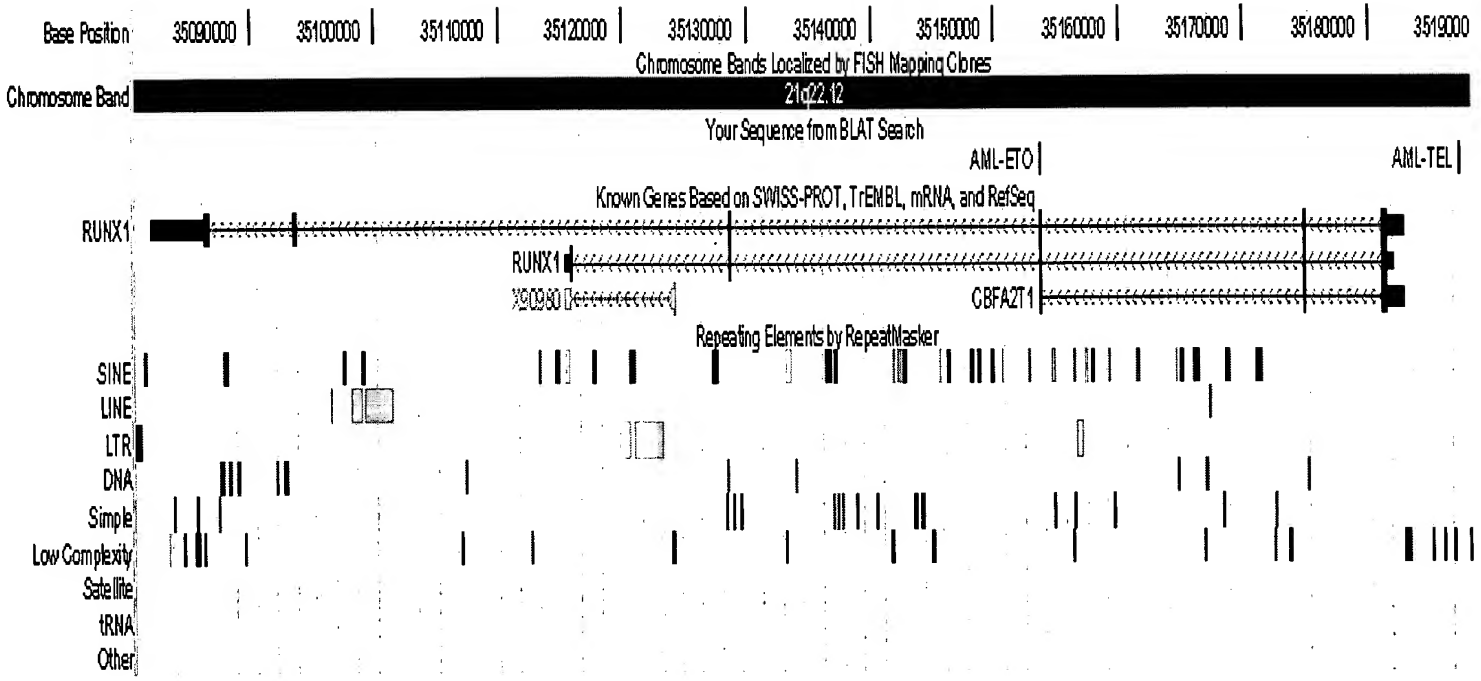

Fig. A. Distribution of repetitive sequences in AML1, designated as RUNXI in official HUGO gene nomenclature, and locations of known breakpoints AML-ETO and AML-TEL.

Accordingly, it cannot be said that Tanaka anticipates the claims, as presently amended.

Finally, during the interview, the number of potential probes that had at least 2000 bp and that were "single copy" as defined in the present application was estimated by applicants to be about 150,000. Applicants emphasize that this is the number of potential probes and not the number of repetitive sequences as it is the probes that this application is concerned with and not the repetitive sequences other than the fact that the probes should be free of such repetitive sequences. By limiting the claims to abnormalities that are associated with a pathological condition or predisposition to disease in an individual or their offspring, this number is greatly reduced but it is difficult to estimate how many such probes will remain. The question of whether applicants truly considered that they were the first to practice the currently claimed methods which do not require prehybridizing or cohybridizing the probes with unlabeled repetitive DNA sequences to provide hybridization specificity also arose during the interview. As set forth in the accompanying declaration, the inventors of the present application believe to the best of their knowledge and belief that they were the first to practice the claimed invention. However, they note that several others may be practicing the claimed methods at this time. As noted above, the parent application to this continuation-in-part application resulted in the issuance of U.S. Patent No. 6,828,097, and that patent claimed the methods for selecting probes computationally.

In view of the foregoing, a Notice of Allowance appears to be in order and such is courteously solicited. In the event that issues still remain, the examiner is encouraged to contact the undersigned at 1-800-445-3460. Any additional fee which is due in

connection with this amendment should be applied against Deposit Account No. 19-0522.

Respectfully submitted,

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